ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2005, p. 2407–2411 Vol. 49, No. 6
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.6.2407–2411.2005

Effects of a High-Fat Meal on the Relative Oral Bioavailability of Piperaquine

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Received 22 November 2004/Returned for modification 19 January 2005/Accepted 27 February 2005

Piperaquine (PQ) is an antimalarial drug whose high lipid solubility suggests that its absorption can be increased by a high-fat meal. We examined the pharmacokinetics of PQ phosphate (500 mg given orally) in the fasting state and after a high-fat meal in eight healthy Caucasian volunteers (randomized crossover). Plasma PQ concentration-time profiles were analyzed by using noncompartmental pharmacokinetic analysis. In the fed state, the geometric mean C_{max} increased by 213%, from 21.0 to 65.8 μg/liter ($P < 0.001$). The time of C_{max} was not significantly different between the fasting and fed states. The geometric mean area under the concentration-time curve from zero onward ($AUC_{0-\infty}$) increased by 98%, from 3,724 to 7,362 μg h/liter ($P = 0.006$). The oral bioavailability of PQ relative to the fasting state was 121% greater after the high-fat meal (95% confidence interval, 26 to 216% increase; $P = 0.020$). The side effects, postural blood pressure changes, electrocardiographic corrected QT interval, serum glucose, and other biochemical and hematological indices were similar in the fasting and fed states over 28 days of follow-up.

Piperaquine (PQ) is a bisquinoline antimalarial drug that was first synthesized in the 1950s (10). It was less toxic than chloroquine (25), and its efficacy against chloroquine-resistant strains of *Plasmodium falciparum* led to its widespread distribution in China and Indochina in the 1970s as prophylaxis and treatment (6, 14). With the emergence of PQ-resistant parasite strains, its use declined (4, 13, 20), but the search for a suitable partner drug as part of artemisinin-based combination therapy (ACT) has led to a resurgence of interest in PQ. Fixed dose combinations of PQ with dihydroartemisinin (DHA) are registered and marketed in China and Vietnam (10).

Despite the fact that PQ has been in clinical use for over 30 years, its pharmacokinetics in malaria have only recently been described (16, 17). The disposition of oral PQ given to Cambodian patients in recommended doses was best described by a two-compartment model with first-order absorption. In adults, the absorption half-life ($t_{1/2abs}$), volume of distribution at pseudodistribution equilibrium relative to bioavailability (V_{ss}/F), apparent oral clearance (CL/F), and elimination half-life ($t_{1/2\beta}$) were 9.1 h, 574 liter/kg, 0.9 liter/h/kg, and 543 h, respectively, whereas in children these variables had mean values of 9.3 h, 614 liter/kg, 1.85 liter/h/kg, and 324 h, respectively. The long $t_{1/2abs}$ and high oil-to-water partition ratio of PQ (3) strongly suggest that its absorption is limited by its high lipid solubility. Since the oral bioavailability of other moderate to highly lipid-soluble antimalarial drugs, including mefloquine, atovaquone, and halofantrine, is increased by administration with a high-fat meal (8, 21, 23), we hypothesized that this would also apply to PQ.

The aim of the present study was, therefore, to determine the effects of a high-fat meal on the oral bioavailability of PQ in healthy Caucasian volunteers. Secondary aims were to investigate the pharmacokinetics of PQ in the fed and fasting states and to add to available data relating to adverse effects (19).

MATERIALS AND METHODS

Subjects. Eight healthy Caucasian adults (four male, four female) were recruited. No subject had taken antimalarial drugs in the previous 3 months or had a known allergy to quinolines. Those on regular medications (including oral contraceptives and herbal remedies) were excluded. The study was approved by the Fremantle Hospital and Health Service Human Research Ethics Committee and was registered under the Clinical Trials Notification Scheme with the Therapeutic Goods Administration (Canberra, Australia). Written informed consent was obtained in all cases.

Clinical procedures. Approximately one week prior to recruitment, a full medical history was taken and a physical examination performed. Each subject had a resting 12-lead electrocardiogram. Standard laboratory tests (full blood picture, liver function tests, serum electrolytes, urea and creatinine, serum lipid profile, urinalysis and, in females, a pregnancy test) were performed by standard automated techniques, and subjects were excluded if any abnormality was detected. The study design was a randomized crossover of PQ administration in the fasting and fed states. For each subject, the two PQ doses were separated by >56 days. The physical examination and standard laboratory tests were repeated 1 week before the crossover study.

For each study, subjects fasted overnight for >10 h and abstained from water 1 h before dose administration. A standard dose of PQ (two 250-mg PQ phosphate tablets [Shanghai Tianping Pharmaceutical Co., Ltd., Shanghai, China]; equivalent to 289 mg [539 μmol] of PQ base) was administered either under fasting conditions or within 10 min of finishing a standard high-fat breakfast. The test breakfast contained 150, 250, and 500 to 600 cal from protein, carbohydrate, and fat, respectively (2) and comprised two sausage-and-egg McMuffins, two hash browns, and 300 ml of orange juice from a McDonalds restaurant (fat [53.4 g], protein [47.4 g], and carbohydrate [108.0 g]). The PQ tablets were administered with 250 ml of water for fasting subjects and with 150 ml of the allocated orange juice for fed subjects. Water and food were not permitted for 1 and 4 h after administration, respectively.

Subjects were monitored for the first 24 h after dose administration. An electrocardiogram, and supine and erect blood pressure (BP) were recorded at 0, 8, and 24 h and at 28 days postdose. The electrocardiographic corrected QT interval (QT_c) was calculated as described previously (19). Fasting serum glucose and insulin were measured at 0, 4 (in the fasting study only), and 24 h and at 28 days after drug administration, and fasting serum cholesterol and triglycerides

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were measured at 0 h and at 7 and 28 days. Heparinized samples for plasma PQ assay were obtained at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h and at 2, 4, 7, 14, 28, 35, and 42 days. All samples were centrifuged within 1 h of collection, and the separated serum or plasma samples were stored at −80°C until assayed. Each subject had an additional full blood picture at 28 days, and additional liver function, serum electrolytes, urea and creatinine, serum lipids, and urinalysis at 7 and 28 days.

Each subject was requested to enter side effects on a daily basis in a standard diary, starting a week before drug administration and continuing until the last blood sample (day 42). The diaries contained a list of symptoms reported in previous PQ studies (10), together with spaces for other complaints. Symptoms were to be rated from 0 to 10 on an integer severity scale.

Analysis of piperaquine in plasma. PQ in plasma was assayed by high-performance liquid chromatography as described previously (16), with minor modifications. Briefly, the procedure was amended in the following ways: (i) the mixing time for the initial extraction of PQ from alkalinized plasma was extended from 10 to 20 min, (ii) the HCl/KCl volume in the final back extraction step was decreased from 300 to 200 μl, (iii) a subsequent freeze-thaw step was added, (iv) the Waters Symmetry C_{18} guard column (Waters Australia, Rydalmere, Australia) was replaced with a 5-μm by 3-mm by 4-mm SecurityGuard C_{18} guard cartridge/holder (Phenomenex, Pennant Hills, Australia), (v) polypropylene rather than borosilicate test tubes and auto-sampler inserts were used, (vi) the standard curve range was increased to 2 to 200 μg/liter, and (vii) chromatogram peak heights rather than areas were used for quantitation. Under these conditions, the retention times for PQ and the internal standard chloroquine were 4.8 and 9.9 min, respectively. Within-run accuracy and precision were 98.0% to 102.5% and 1.7% to 7.0%, respectively, over the range 1.5 to 200 μg/liter (2.80 to 373 nmol/liter), while between-run accuracy and precision were 98.6% to 103.7% and 1.7% to 3.9%, respectively, over the range 2.5 to 200 μg/liter (4.67 to 373 nmol/liter). The lower limits of detection (0.5 μg/liter; 0.93 nmol/liter) and quantification (1.5 μg/liter; 2.80 nmol/liter) for PQ in plasma were lower than those achieved with our original method.

The possible effects of the high-fat meal on the plasma matrix and piperaquine assay were also considered in the method validation. Previous studies with an oral 50-g fat load in control subjects have shown that plasma triglyceride levels remain unchanged over the ensuing 6 h (22), an observation confirmed in the present subjects (data not shown).

Data analyses. Noncompartmental pharmacokinetic analysis was performed by using the Kinetica 4.3 software (Innaphase Corp., Philadelphia, Pa.). The elimination rate constant (L_z) and computed last datum point were calculated by log-linear regression analysis of the last six data pairs (1 week and onwards). Elimination half-lives ($t_{1/2\beta}$) were calculated as $t_{1/2\beta} = \ln 2/L_z$. The maximum plasma concentration (C_{max}) and the time at which it occurred (T_{max}) were interpolated from the primary plasma concentration-time data. The area under the concentration-time curve to the last datum point ($AUC_{0\text{–last}}$) and area under the first moment curve to last datum point ($AUMC_{0\text{–last}}$) were calculated by the mixed log-linear trapezoidal rule. Area under curve to infinity ($AUC_{0\text{–}\infty}$) and area under the first moment curve to infinity ($AUMC_{0\text{–}\infty}$) were extrapolated by using the computed last datum point and L_z.

For each subject, averaged elimination phase half-lives (between the two studies) were used for deriving L_z, $AUC_{0\text{–}\infty}$, and $AUMC_{0\text{–}\infty}$. The mean residence time (MRT) was calculated as MRT = $AUMC_{0\text{–}\infty}/AUC_{0\text{–}\infty}$. Dose (289 mg of PQ = 500 mg of PQ phosphate = 539 μmol of PQ) was expressed relative to body weight. CL/F and apparent volume of distribution in the elimination phase relative to bioavailability (V_z/F) were calculated as Dose/$AUC_{0\text{–}\infty}$ and (CL/F)/L_z, respectively, and normalized to body weight. V_{ss}/F was calculated as (CL/F) × MRT and divided by weight. Bioavailability with the high-fat meal was calculated relative to that when fasting as: F = 100 × (fed $AUC_{0\text{–}\infty}$/fasting $AUC_{0\text{–}\infty}$).

Statistical analysis was performed by using SigmaStat 3.1 (SPSS, Inc., Chicago, IL). The data are summarized as mean (± the standard deviation) unless otherwise specified. Repeated measures analysis of variance (RM-ANOVA) or RM-ANOVA on ranks and Dunnett's test post hoc were used to assess differences in serum glucose, QT_c, heart rate, postural blood pressure changes, serum cholesterol, and serum triglycerides across time. When fasting and fed states were compared, C_{max} and AUC data were log transformed (1) before comparison by using a paired *t* test. These data are presented after reverse transformation. A two-tailed level of significance of $P < 0.05$ was used throughout. Bioequivalence of the formulation in the fed and fasted states was also assessed by using the standard U.S. Food and Drug Administration (FDA) test (1). This test for establishing bioequivalence consists of analyzing log-transformed AUC data and comparing the 90% confidence interval (CI) against the acceptable lower and upper limits of −20% and +25% between geometric means for bioequivalence.

TABLE 1. Pharmacokinetics of oral piperaquine in eight volunteers when fasting and after a high-fat meal

Parameter	Mean ± SD[a]	
	Fasting	High-fat meal
C_{max} (μg/liter)[b]	21.0 (14–31.4)	65.8 (38.7–112.0)[c]
T_{max} (h)	6.8 ± 4.7	3.5 ± 1.4
$AUC_{0\text{–last}}$ (μg h/liter)[b]	2,818 (1,566–5,070)	5,821 (3,436–9,861)[d]
$AUC_{0\text{–}\infty}$ (μg h/liter)[b,e]	3,724 (2,193–6,324)	7,362 (4,487–12,078)[d]
AUC_{extrap} (%)	24 ± 6	20 ± 8
L_z (liter/h)	0.00150 ± 0.00034	0.00156 ± 0.00054
$t_{1/2\beta}$ (h)	488 ± 131	501 ± 191
MRT (h)	621 ± 129	598 ± 162
CL/F (liter/h/kg)	1.14 ± 0.46	0.60 ± 0.39
V_z/F (liter/kg)	818 ± 366	451 ± 380
V_{ss}/F (liter/kg)	716 ± 334	365 ± 284

[a] Unless otherwise specified.
[b] Geometric mean (standard deviation range).
[c] $P < 0.001$.
[d] $P = 0.006$.
[e] Calculated by using the average $t_{1/2\beta}$ value from the high-fat and fasting studies.

RESULTS

The median age, body weight, and body mass index for the eight volunteers were 21 years (range, 19 to 42 years), 68.8 kg (range, 63.5 to 95.0 kg), and 25.1 kg/m^2 (range, 19.1 to 33.8 kg/m^2), respectively. The median PQ dose administered to the 8 volunteers was 4,199 μg base/kg (range, 3,039 to 4,546 μg base/kg).

Pharmacokinetic parameters are summarized in Table 1. Comparison of the fasting and fed states showed that the geometric mean C_{max} increased from 21.0 to 65.8 μg/liter (213% increase, 95% CI = 117 to 352%), the geometric mean $AUC_{0\text{–last}}$ increased from 2,818 to 5,821 μg h/liter (107% increase, 95% CI = 33 to 221%), and the geometric mean $AUC_{0\text{–}\infty}$ increased from 3,724 to 7,362 μg h/liter (98% increase, 95% CI = 30 to 201%; $P < 0.01$ in each case). The 90% CI for the increase in geometric mean $AUC_{0\text{–}\infty}$ was 42 to 177%, indicating that the formulation was not bioequivalent by FDA standards between the fed and fasting states. The oral bioavailability of PQ was 121% greater after the high-fat meal versus the fasting state (95% CI = 26 to 216% increase; $P = 0.020$). Mean T_{max} values were not significantly different (fasting [6.8 h] versus fed [3.5 h]) with a mean increase of −3.4 h (95% CI = −8.0 to 1.2 h; $P = 0.11$). Mean $t_{1/2\beta}$ values were not significantly different (fasting [488 h] versus fed [501 h]; 95% CI = −201 to 228 h; $P = 0.89$). Typical plasma PQ-time profiles in three subjects are shown in Fig. 1 (left-hand panels). Secondary peaks were commonly seen during the first 15 h postdose (Fig. 1, right-hand panels).

Hematological indices, hepatorenal function, and urinalysis did not change as a result of PQ administration (data not shown). Changes in heart rate, BP, QT_c interval, serum glucose, and serum lipids before and after drug administration are summarized in Table 2 for the fasting arm of the study. There was some attenuation of the postural rise in systolic BP on standing at 24 h and 28 days compared to the baseline. There were no significant changes in the QT_c, glucose, or serum lipid profile during follow-up. Similar changes were seen in the fed arm (data not shown).

Side effects reported during the fasting and fed studies were similar. One volunteer reported mild to moderate nausea for a

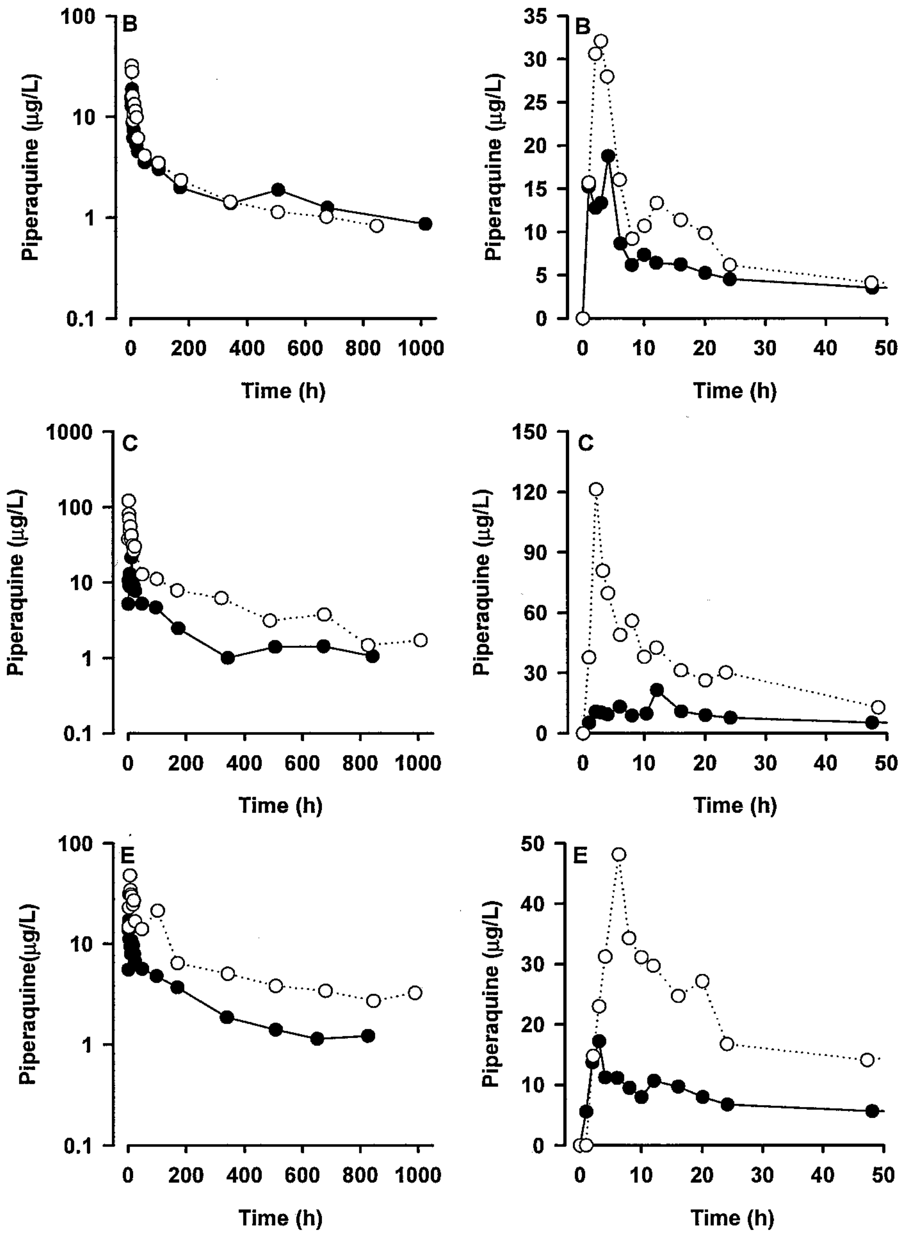

FIG. 1. Typical plasma piperaquine concentration-time profiles (left panel, up 1,000 h [ca. 42 days] after dose; right panels, first 50 h after dose) in three representative volunteers (identity code B, C, and E) when fasting (●) and after a high-fat meal (○).

few days after drug administration. Moderate to severe drowsiness and fatigue were reported by several volunteers throughout the study, including during the week prior to dosing. Headache and dizziness was uncommon, although one of each at moderate severity was reported on the day of drug administration. All other symptoms (constipation, diarrhea, visual/auditory disturbances, palpitations, and rash/itch) were either not reported or were reported at low frequency and severity (score of ≤4). In no case were the symptoms severe enough to require medical attention.

DISCUSSION

The present data demonstrate that, relative to the fasting state, the oral bioavailability of PQ is approximately doubled by a high-fat meal. We also gathered safety data from our healthy volunteers and confirmed that PQ administration does not produce significant metabolic or cardiovascular effects. The drug was generally well tolerated, although subjective symptom reporting indicated that mild nausea, abdominal pain, headache, and dizziness occurred transiently after PQ administration.

There are few studies examining the effects of food on antimalarial drug disposition. Very high lipid solubility is often associated with low bioavailability in the fasting state (11) and an increase in absorption when the drug is coadministered with a fatty meal (24). In the case of antimalarial drugs, a high-fat meal increased the C_{max} and AUC of mefloquine (log P_{10} = 2.9) by 73 and 40%, respectively (8), while there were much

TABLE 2. Selected physiological and biochemical measures in the 15 volunteers during the fasting piperaquine pharmacokinetic study

Parameter[a]	Mean value ± SD at:					
	0 h	4 h	8 h	24 h	7 days	28 days
Heart rate (beats/min)	60 ± 11		64 ± 14	66 ± 16		68 ± 13
Postural systolic BP change[a]	19 ± 14		9 ± 8	3 ± 13[b]		4 ± 7[b]
Postural diastolic BP change[a]	9 ± 9		5 ± 9	8 ± 4		6 ± 4
QT_c interval ($ms^{0.5}$)	391 ± 27		393 ± 24	393 ± 37		399 ± 30
Glucose (mmol/liter)	4.7 ± 0.3	4.7 ± 0.2		5.0 ± 0.2		4.8 ± 0.3
Serum total cholesterol	4.4 ± 0.6				4.4 ± 0.7	4.5 ± 1.1
Serum triglycerides (mmol/liter)	0.6 ± 0.3				0.7 ± 0.2	0.8 ± 0.3

[a] BP change = erect BP − supine BP.
[b] Dunnett's test versus 0 h, $P < 0.05$.

greater increases in these parameters in the case of both atovaquone (log P_{10} = 6.2) (430 and 230%, respectively) (23) and halofantrine (log P_{10} = 8.9) (560 and 190%, respectively) (21). PQ also has a high lipid solubility (log P_{10} = 6.2), and our finding of significant increases in C_{max} (238%), $AUC_{0\text{–last}}$ (97%), and $AUC_{0\text{–}\infty}$ (93%) after the high-fat meal are consistent with these previous reports (8, 21, 23).

When used to treat falciparum malaria, PQ is conventionally given as four equal doses of between 2.8 and 10.8 mg base/kg (equivalent to a total of 11 to 43 mg base/kg) (10). The dose selected for the present study (4.2 mg base/kg) was in the lower half of this range. If the food-related changes in C_{max} can be extrapolated to a typical adult patient with malaria receiving a conventional treatment regimen, peak PQ concentrations would increase from ca. 250 μg/liter (17) to levels approaching 750 μg/liter. This could increase the risk of acute toxicity, including gastrointestinal side effects. Nevertheless, an increase in bioavailability might also result in a more predictable plasma concentration profile and perhaps even allow a reduction in PQ dose and treatment cost. In acute malaria, it might be possible to administer PQ with fat (e.g., cow's milk). However, new PQ-containing formulations might also achieve enhanced bioavailability and reduced dose by manipulating the lipid solubility and absorption profile of PQ.

We chose to use a tablet formulation containing only PQ in order to avoid the complications of a second antimalarial drug component such as an artemisinin derivative. Although it is possible that a different formulation and/or a second drug might alter the high-fat meal effect that we have seen, only further studies can answer this question. However, the mean fasting elimination half-life (488 h) and oral clearance (1.14 liter/h/kg) of PQ in the present study were similar to those in an earlier report with PQ-dihydroartemisinin ACT in patients with uncomplicated malaria (17).

Consistent with data from earlier studies in patients with malaria (10), we did not find any significant changes in biochemical, hematological, or cardiovascular indices. We conclude that the risk of PQ-induced hypoglycemia, in contrast to related compounds such as quinine and mefloquine (9) and consistent with the results of clinical studies (10), is minimal.

Although we relied on subjective symptom reporting to identify PQ side effects, we used a 1-week run-in to give a baseline symptom profile for comparison purposes. For most symptoms, there was no increase in frequency or severity after PQ administration. However, one case each of moderate severity for nausea, headache, and dizziness occurred on the day of dosing. Previous studies in larger numbers of patients with malaria taking greater PQ doses have reported that nausea and vomiting are common (5, 12, 13, 15, 17), but these symptoms also result from the infection itself. Overall, PQ appears to be well tolerated.

The secondary peaks seen in plasma PQ concentration-time profiles in both fasting and fed studies suggest that PQ may undergo enterohepatic recycling and/or be subject to multisector intestinal absorption. In support of this hypothesis, data from animal studies show that PQ and/or its metabolites are excreted in bile (7). The related drug mefloquine is also known to undergo enterohepatic recycling (18).

We have demonstrated that the absorption of PQ is approximately doubled by coadministration with a high-fat meal. However, currently recommended doses of PQ as part of ACT are highly effective when given to fasting patients (10, 17). It does not seem necessary, therefore, to give PQ with fat, a strategy that could, in any case, increase the incidence and/or severity of common side effects. The finding of secondary peaks in the concentration-time profile suggests that enterohepatic recirculation may be important in the disposition of PQ and highlights the need for studies of its metabolism in humans.

ACKNOWLEDGMENTS

I.-K.S. was the recipient of a University of Western Australia Jean Rogerson Scholarship.

We gratefully acknowledge the assistance of Paul Chubb for performing the biochemical assays.

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